How 25 years of psychosocial research has contributed to a better understanding of the links between depression and diabetes

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How 25 years of psychosocial research has contributed to a better understanding of the links between depression and diabetes

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Abstract

This narrative review of the literature provides a summary and discussion of 25 years of research into the complex links between depression and diabetes. Systematic reviews have shown that depression occurs more frequently in people with type 1 or type 2 diabetes compared with people without diabetes. Currently, it remains unclear whether depression is also more common in people with impaired glucose metabolism or undiagnosed type 2 diabetes compared with people without diabetes. More prospective epidemiological research into the course of depression and an exploration of mechanisms in individuals with diabetes are needed. Depression in diabetes is associated with less optimal self-care behaviours, suboptimal glycaemic control, impaired quality of life, incident micro- and macrovascular diseases, and elevated mortality rates. Randomized controlled trails concluded that depression in diabetes can be treated with antidepressant medication, cognitive–behavioural therapy (individual, group-based or web-based), mindfulness-based cognitive therapy and stepped care. Although big strides forward have been made in the past 25 years, scientific evidence about depression in diabetes remains incomplete. Future studies should investigate mechanisms that link both conditions and test new diabetes-specific web- or app-based interventions for depression in diabetes. It is important to determine whether treatment or prevention of depression prevents future diabetes complications and lowers mortality rates.

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Introduction

Depression is a serious and common psychiatric condition that severely impairs the quality of life of those who suffer from the disease. It is a heterogeneous disorder that is diagnosed on the basis of clinical symptoms and the extent of functional deterioration associated with these symptoms. The syndrome comprises emotional symptoms (depressed mood, irritability, anhedonia, feelings of guilt), cognitive symptoms (depressed thoughts, suicidal ideation, feelings of worthlessness, concentration problems), and behavioural or somatic symptoms (hyperphagia or hypophagia and change in weight, hypersomnia or insomnia, psychomotor retardation or activation, fatigue) [1]. A biological marker for depression does not exists. According to Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), diagnosis of a major depressive episode can be made when at least five of nine symptoms, including at least one core symptom, are present for at least two weeks or longer. Because different combinations of depression symptoms can lead to a diagnosis, various clinical profiles of depression exist. Depending on the symptom severity and symptom count, a depressive episode can described as severe, moderate or mild. The course of depression is described as first episode, recurrent episode or chronic depression [1].

In the large World Health Surveys study [2] conducted in 245 404 participants from 60 countries, 9% (95% CI 7.3–11.3) of respondents with diabetes also had depression, 11% (95% CI 9.1–12.3) with arthritis were also depressed, as were 15% (95% CI 12.9–17.2) with angina; persons with asthma had the highest prevalence of depression at 18% (95% CI 15.9–20.3). Thus, the prevalence of depression in individuals with a chronic condition is significantly higher than in those without (3.2%, $P < 0.0001$).

Depression is also perhaps the most commonly and longest studied psychiatric problem in connection with diabetes. In

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What's new?

- By 1995, a few epidemiological studies had concluded that depression was more common in people with diabetes than in those without. However, intervention studies were lacking and longitudinal studies were scarce.
- Over the past 25 years, research has confirmed the bidirectional relationship between depression and type 2 diabetes.
- Depression in diabetes impairs quality of life and is associated with less effective self-management, a higher risk of diabetes complications and higher mortality rates.
- Depression in diabetes can be treated effectively with psychological and pharmacological therapy.
- Awareness of depression in people with diabetes should be raised and adequate mental health care should be available to treat depression.
- Future studies should elucidate the biological and behavioural mechanisms that link depression and diabetes and test the long-term effects of treatment.

the 17th century, the physician Thomas Willis, founding Fellow of the Royal Society, noted that diabetes seemed to be more common in people who had experienced sadness or long sorrow [3]. Over the past 30 years, the number of studies in this area has increased exponentially. A simple literature search on 23 September 2019 entering the words 'diabetes AND depression' into PubMed yielded 1069 hits for the period 1900–1994. The same search, but for the 25-year period 1995–2019, resulted in a 10-fold higher result of 11 659 hits. In this article, we review the past 25 years of research into the links between type 1 or type 2 diabetes and depression.

What we knew in 1995

A systematic review, published in 1993, described the prevalence of depression in adults with diabetes based on a total of 20 studies [4]. Both clinical and community-based samples were included and nine of the studies had a control group. The reported prevalence of diagnosed depression in people with diabetes ranged between 9% and 27% (average 14%) in studies with a control group, and between 11% and 20% in uncontrolled studies (average 15%) [4]. These percentages were threefold higher than the rates of major depression found in samples of adults without diabetes. Investigations using depression symptom scales reported a range of clinically significant depressive symptomatology in people with diabetes of between 22% and 60% (average 32%) in controlled studies, and between 10% and 28% (average 20%) in uncontrolled studies. In the mid-1990s, little was known about the course of depression in diabetes. In 1992, Lustman *et al.* [5] concluded that only one systematic follow-up study was available. No studies had examined depression as a risk factor for type 2 diabetes or for diabetes complications, although based on three studies, Alan Jacobson commented in December 1993 [6],

> [. . .] it is reasonable to assume that this is a bidirectional relationship with glycaemic control problems and depression affecting each other in reciprocal fashion. Thus, depression may be a risk factor for the progression of the consequences of poor metabolic control, i.e., the microvascular and neuropathic complications of diabetes.

In those days, randomized controlled trials (RCTs) testing pharmacological or psychological interventions for depression in diabetes were lacking. In 1992, Lustman *et al.* wrote [5],

> Pharmacotherapy of depression may improve both mood and glucose regulation in diabetes, although controlled studies of the efficacy of psychotherapy and pharmacotherapy for depression in diabetes are not yet available.

What we now know after 25 years of research into diabetes and depression

Depression as a risk factor for type 2 diabetes

The first prospective investigation testing depression as a risk factor for the development of type 2 diabetes was published in 1996 [7]. In this study, which included 1715 participants without diabetes at baseline, diagnosed major depression, but not milder forms of depression or other forms of psychiatric disorder, seemed to predict the onset of type 2 diabetes [although the estimated relative risk (RR) was not significant: 2.23; 95% confidence interval (CI) 0.90–5.55] [7]. Ten years later, the first meta-analysis was published based on data from nine longitudinal studies, showing that depressed adults have a 37% higher odds of developing type 2 diabetes [8]. A later meta-analysis based on 23 longitudinal studies, involving 424 557 participants, with a mean follow-up duration of 8.3 years, and 19 977 cases of incident diabetes, confirmed these findings. The incidence of diabetes was higher in people with depression compared with those without (0.72% vs. 0.47% yearly), with an unadjusted and adjusted risk (95% CI) of 1.56 (1.37–1.77) and 1.38 (1.23–1.55), respectively [9].

The prevalence of depression in diabetes

Since 1995, several systematic reviews have summarized the results of a considerable number of investigations with a cross-sectional design that aimed to determine the prevalence of depression in individuals with diabetes [10–15]. In most

papers, self-report measures of depression were utilized: few used a diagnostic interview for the diagnosis of a mood disorder. In the case–control studies, the risk of depression was two times higher in comparison with individuals without diabetes in studies that used self-report or a diagnostic interview [10]. Research teams that aimed to assess the prevalence of depression while using a self-report measure generally found a two- to threefold higher prevalence of depression (i.e. a high depression symptom severity) compared with studies that used structured diagnostic interviews (i.e. a diagnosed mood disorder) [10].

Buchberger *et al.* [15] conducted a systematic review of 14 papers and concluded that a high level of depressive symptom severity was present in almost one-third of children or adolescents with type 1 diabetes. Depression was more than three times as common in adults with type 1 diabetes (12% vs. 3%) and nearly twice as common in type 2 diabetes (19% vs. 11%) in comparison with individuals without diabetes [14]. A key limitation of this review was that it mixed studies that utilized different methods to measure depression [14]. A further systematic review that meta-analysed 12 studies also concluded that depression was more common in people with diagnosed type 2 diabetes in comparison with those with a normal glucose metabolism [13]. The paper also reported that the odds of depression were not higher in individuals with screening diagnosed type 2 diabetes or impaired glucose metabolism (pre-diabetes) compared with those with normal glucose metabolism [13]. A Chinese study also concluded that, compared with people with normal glucose regulation (n = 120 458), people with diabetes (n = 24 251) had higher odds of probable diagnosis of depression (1.61, 95% CI 1.39–1.87) and sub-threshold depression [odds ratio (OR) = 1.14, 95% CI 1.06–1.24], whereas newly diagnosed diabetes (n = 24 826) or impaired glucose regulation (n = 59 512) were not associated with depression [16].

Two other cross-sectional studies have confirmed this [17,18]. The LifeLines Study, another large study in this area, analysed data from more than 90 000 individuals, including from a diagnostic interview and an assessment of fasting glucose. That study reported that both long-existing and recently diagnosed diabetes (OR 1.8, 95% CI 1.3–2.6; P = 0.001) were associated with an increased risk of depression [19]. Individuals with impaired fasting glucose (pre-diabetes) also had an increased risk of depression compared with people without diabetes (OR 1.2–1.6, dependent on how pre-diabetes was defined) [19].

Some symptoms of depression such as fatigue, disturbed sleep or altered eating behaviours can also be symptoms of suboptimal glycaemic control. Harding *et al.* [20] examined the extent to which depression prevalence was dependent on the amount of depression–diabetes symptom overlap (i.e. items within symptom dimensions) and sample characteristics. In their review, Harding *et al.* included 147 studies that used 24 validated depression questionnaires and found that diabetes–depression symptom overlap did not affect prevalence rates. Furthermore, studies that used a questionnaire with a higher percentage of symptoms of anhedonia, cognition, negative affect and disturbed sleep, and a lower proportion of somatic symptoms reported a higher prevalence of depression [20].

Depressive symptom questionnaires have also been shown to pick up diabetes distress, which may sometimes be the key issue requiring attention. For example, Fisher *et al.* [21] found a high percentage of false positives when they compared the Patient Health Questionnaire Depression Scale (PHQ-8) with a structured diagnostic interview, and an unexpectedly low rate of major depression in persons with type 1 diabetes. They also found that many people had high levels of diabetes distress and the authors concluded that emotional problems are often labelled as depression in adults with type 1 diabetes although the symptoms may be better regarded as diabetes–distress, resulting from having to manage a chronic, demanding condition, or be due to other life stressors. These persons with diabetes in particular, perhaps need treatments that aim at reducing diabetes distress and/or target other life stressors rather than focus on depression [21].

Depression in diabetes: results from prospective studies

Only a few prospective investigations have studied the course of depression in individuals with diabetes. A large study undertaken by Kampling *et al.* [22] looked at the course of depression over a period of 5 years in adolescence and early adulthood (17–40 years) with recently diagnosed (< 3 months) of type 1 diabetes. This longitudinal study made use of diagnostic interviews during the baseline assessment. Depression was measured by self-report only at follow-up assessments as the diagnostic interviews were not repeated. In 6% of persons with recently diagnosed type 1 diabetes, a comorbid major depression was also diagnosed, whereas 8% appeared to have a comorbid anxiety disorder [22]. This means that healthcare providers can expect that one in ten people with recently diagnosed type 1 diabetes will have a mood or anxiety disorder. In the 5-year follow-up period, the majority (79%) of these young people with diabetes did not experience depressive symptoms at any assessment, 7% reported elevated depression scores that showed improvement over time, while 14% had worse depressive symptoms during follow-up [22].

A systematic review with meta-analysis of 11 longitudinal studies showed that, compared with individuals without diabetes, people with type 2 diabetes have a 24% increased risk of developing depression [23]. A later systematic review with meta-analysis of 16 longitudinal studies reported a higher pooled OR for incident depression among respondents with diabetes (1.34, 95% CI 1.14–1.57, χ^2 = 76.65, I^2 = 80.4%; P < 0.001), again confirming diabetes as a risk factor for depression [24]. Nefs *et al.* [25] conducted a 3-year longitudinal study of 2460 people with type 2 diabetes and

examined the course (incidence, recurrence/persistence) of depressive symptoms by self-report questionnaire in a primary care setting. Among individuals with type 2 diabetes, 26% appeared to have at least one elevated depression score during the 3-year study. Incident elevated depression at one of the follow-up assessments was present in 14% of participants, while recurrent or persistent depression was evident in 66% [22]. Depression in the past was the strongest risk factor for a high depression score in the future [25].

Depression in diabetes and long-term health outcomes

Depression substantially impairs quality of life in people with diabetes [26]. Meta-analyses of longitudinal studies also showed that individuals with diabetes and depression have an elevated risk of developing not only microvascular, but also macrovascular complications, a higher risk of cognitive decline and also higher mortality rates [27,28]. A systematic review with meta-analysis of 16 longitudinal diabetes studies showed that, after adjustment for demographic variables and micro- and macrovascular complications, baseline depression was associated with an increased risk of all-cause mortality [hazard ratio (HR) 1.46, 95% CI 1.29–1.66] and cardiovascular mortality (HR 1.39, 95% CI 1.11–1.73] [28]. In the meta-analysis, heterogeneity across studies was high for all-cause mortality, but relatively low for cardiovascular mortality. A comparison between type 1 and type 2 diabetes could not be made because only one study focused on type 1 diabetes specifically [28].

Another systematic review of 22 longitudinal studies investigated the relationships between depression and diabetes complications [27]. Sixteen papers investigated associations between depression and the incidence of diabetes complications. A high baseline depression score was linked to incident macrovascular (HR 1.38, 95% CI 1.30–1.47) and microvascular disease (HR 1.33, 95% CI 1.25–1.41) complications. Six longitudinal studies showed that persons with diabetes complications had a higher risk of developing a depressive disorder (HR 1.14, 95% CI 1.07–1.21) [27]. So, not only is the association between diabetes and depression bidirectional, but the same holds true for associations between depression and diabetes complications. In both cases, the risk of developing type 2 diabetes or diabetes complications in people with depression is higher than the risk of developing depression in people with diabetes or its complications [27].

Suicidal ideation is an important and burdensome symptom of depression. A recent systematic review of 17 studies evaluated the risk of suicidality among people with diabetes. Seven studies reported data on suicidal death that was confirmed by either International Classification of Diseases (ICD) codes or examination of the death certificate. Five studies focused on suicide attempts or self-harm. Nine cross-sectional studies examined suicidal ideation [29]. People with diabetes were more often suicidal than people without diabetes. The pooled OR values for suicidal ideation, attempted suicide and completed suicide were 1.89 (95% CI 1.36–2.63), 1.45 (95% CI 1.07–1.96) and 1.85 (95% CI 0.97–3.52), respectively [29].

Mechanisms linking depression and diabetes

The mechanisms that explain why depression is associated with poor outcomes in diabetes are unclear and understudied in individuals with type 1 diabetes. Current hypotheses distinguish mechanisms at a behavioural level, such as the burden of disease hypothesis and adverse lifestyle behaviour, and at a biological level, involving the effects of hyperglycaemia, hypothalamic–pituitary–adrenal (HPA) axis deregulation, low-grade inflammation and microvascular dysfunction [29–37]. From a behavioural perspective, depression can impair several different self-care behaviours; a systematic review of 47 studies concluded that depression in people with diabetes was linked with less optimal self-care behaviours, lower diet quality, less optimal medication use and less frequent glucose monitoring, and lower appointment keeping [30].

Based on the common ground hypothesis, several biological mechanisms have been associated with poor diabetes outcomes in people with diabetes and depression [31–37]. This hypothesis assumes that diabetes and depression have common denominators, including genetic factors, overactivation of the innate immune system or dysregulation of the HPA axis. These common grounds could independently lead to insulin resistance and an increased risk of type 2 diabetes, cardiovascular disease and depression.

The strongest evidence for a shared genetic mechanism comes from twin registries that can disentangle genetic from shared environmental risk factors. Kan *et al.* [35] used population-level data from the Swedish (n = 68 606) and Danish (n = 95 403) twin registries and found that the phenotypic correlation between type 2 diabetes and depression was modest in both samples, but also that genetic background could explain the co-occurrence of diabetes and depression. In a later study, based on data from the CHARGE consortium (n = 51 258), and DIAGRAM consortium (n = 34 840 people with diabetes and 114 981 controls), the genetic correlation between depressive symptoms and type 2 diabetes was estimated using single-nucleotide polymorphism (SNP)-based heritability [36]. In contrast to the twin studies, linkage disequilibrium score regression analyses showed no significant genetic correlation between depression and type 2 diabetes or glycaemic traits [36]. Another study investigated the shared aetiology between type 2 diabetes and major depressive disorder using Mendelian randomization (MR) in a Scottish population-based sample of 21 516 people [37]. Causality and genetic overlap between type 2 diabetes and major depression were assessed using polygenic risk scores that were obtained from

the largest available genome-wide association study summary statistics to date [37]. No single type 2 diabetes risk SNP was associated with major depression in the MR analyses. In the same way, the results for the polygenic risk scores analyses and also the linkage disequilibrium score regression analyses showed no consistent evidence of genetic overlap between major depression and type 2 diabetes [37]. However, the lack of genetic studies that explain the link between depression and diabetes does not reject the common ground hypothesis, as we know that the genetic predisposition of both diabetes and depression is modest. These findings emphasize that the biological clues appear to be the result of acquired behavioural and environmental factors, more than genetic susceptibility.

In favour of this notion, Herder and Hermanns [33] provide a narrative overview of epidemiological studies that have investigated the associations between inflammatory biomarkers and depressive symptoms or diagnosed depression in people with diabetes. In people with type 1 diabetes, the evidence suggests that higher levels of interleukin (IL)-1, IL-1 receptor antagonist (IL-1RA), IL-6, high-sensitivity C-reactive protein (hsCRP), and soluble intercellular adhesion molecule 1 may be related to depressive symptoms or, for hsCRP, lower treatment response. For people with type 2 diabetes, IL-1RA, hsCRP, chemokine (C-C motif) ligand 2 and adiponectin or its isoforms were associated with depressive symptoms in two or more studies [33]. Positive associations were also reported between IL-1β, IL-6 and IL-18 with depressive symptoms or diagnosed depression in single studies. The authors concluded that the number of studies in this area did not allow for meta-analysis.

Furthermore, the vascular depression hypothesis may be especially relevant in type 2 diabetes because diabetes is strongly linked to microvascular and also cerebrovascular damage. In addition, emerging evidence shows that markers of cerebral small vessel disease (for example, white matter hyperintensities and lacunar infarctions) are associated with incident depression [34]; this fuels the hypothesis that vascular damage in frontal and subcortical regions of the brain, which are involved in mood regulation, may lead to depression in later life [38]. Further evidence is needed to substantiate the role of microvascular dysfunction in comorbid diabetes and depression.

Hoogendoorn *et al*. [39] recently discussed the results of studies that investigated whether depression and type 2 diabetes can both result from dysregulation of homeostatic brain–body pathways. In their study, the authors focus on the role of the HPA axis and also the brain–gut–microbiome (BGM) axis, and conclude that this dysregulation may be a key intervention target for depression, type 2 diabetes and their comorbidities. The authors also conclude that there is a need for better studies that critically examine the potential role of BGM axis. Future studies should thus carefully investigate whether dysregulation of the BGM or HPA axes is causally related to depressed mood, stress or the development of type 2 diabetes [39].

Antidepressant use and diabetes

Barnard *et al*. [40] published a systematic review that investigated whether antidepressant use was associated with diabetes. The review is based on 21 observational studies, comprising five case–control, four cross-sectional and 12 cohort studies. The authors concluded that there was some evidence that antidepressant use is an independent risk factor for type 2 diabetes. They also described how larger, more recent studies that could include larger numbers of participants that received antidepressant medication suggest that any risk is relatively small [40,41]. In a very large study of 138 659 women and 29 776 men, data from three large studies were pooled to assess the risk of diabetes associated with antidepressant medication use [41]. Use of antidepressant medications was assessed biennially, and type of antidepressant medication was recorded at later follow-up measurements. Women were more often prescribed antidepressant medication than men. In the adjusted multivariable analyses, baseline antidepressant use did not predict incident diabetes, but use of any antidepressant medication was associated with an elevated risk of diabetes in models that were adjusted for differences in age (pooled HR 1.68, 95% CI 1.27–2.23); these results suggest that recent use of antidepressant medication might be more relevant to an elevated diabetes risk [41]. In women, the average absolute difference in risk between non-users and those taking antidepressant medication was 2.87 per 1000 person-years. After adjustment for diabetes risk factors, elevated cholesterol, hypertension and BMI, the association became smaller (HR 1.17, 95% CI 1.09–1.25) [36]. This may suggest that use of antidepressant medication can contribute to diabetes risk via an increase in body weight. New high-quality long-term prospective studies on the effects of individual antidepressants are now warranted [40]. The lack of specificity in relation to individual antidepressant drugs raises the possibility that any association with diabetes could also result from detection bias, as people with depression may receive more frequent medical attention [42]. This hypothesis is supported by results from the Whitehall II study, showing that incident, physician-diagnosed diabetes was more frequent among users of antidepressants compared with non-users, whereas use of antidepressant medication was not linked with undiagnosed diabetes [42].

Screening for depression in people with diabetes

Depression often remains undetected in diabetes and several diabetes guidelines recommend screening for depression [43]. A systematic review of 21 studies identified that the Center for Epidemiologic Studies Depression Scale (CES-D) and the PHQ-9 are most frequently used in diabetes research [43].

The CES-D appeared to have the highest sensitivity, whereas the PHQ-9 had the highest specificity [43]. It is important to emphasize that screening for depression in diabetes is only effective if it is embedded in a comprehensive healthcare system that offers subsequent diagnosis and appropriate treatment options [44]. Without this being in place, screening is unethical. Potential harms of screening also include the risk that diabetes-distress is labelled as depression, the stigma associated with depression, or possible discrimination by insurance companies. The use of a depression screener could also result in staff doing a routine procedure and 'box tick'. It can lead to the impression that psychological issues are discussed, although other psychological problems such as disturbed eating, sleeping problems, elevated diabetes distress or treatment dissatisfaction are not discussed. It is also important that diabetes care professionals do not confuse a high score on a questionnaire with a need for psychological care. Asking the question: 'Do you want professional support for these problems' might be as important as knowing whether the person with diabetes is depressed. Collaboration between healthcare professionals is a prerequisite for implementation of these strategies.

The treatment of depression in diabetes

A meta-analysis of 14 RCTs, published in 2010, tested different interventions targeting depression in people with diabetes [45]. The authors concluded that treatment was effective in terms of reducing depression symptoms (−0.512; 95% CI − 0.633 to − 0.390) and that overall effect of all interventions on clinical impact was moderate (−0.370; 95% CI − 0.470 to − 0.271). The largest effect of psychotherapeutic interventions was seen when combined with a diabetes self-management intervention (−0.581; 95% CI − 0.770 to − 0.391) but was more moderate for antidepressant medication (−0.467; 95% CI − 0.665 to − 0.270). Collaborative care interventions for depression in diabetes that provide stepped care in a primary care setting, offering a choice of starting with psychotherapy or pharmacotherapy, yielded an effect size of − 0.292 (95% CI − 0.429 to − 0.155). Except sertraline, antidepressant medication and collaborative care had no effect on glycaemic control [45].

Another systematic review, published a few years later, evaluated the effectiveness of cognitive–behavioural therapy (CBT) on at least one of: HbA_{1c}, depression, anxiety, diabetes-related distress or quality of life in adults with type 1 or type 2 diabetes [46]. Based on the results of 12 RCTs, the authors concluded that CBT is effective in reducing depression and also short- and medium-term, but not long-term, HbA_{1c}. CBT improved short- and medium-term anxiety and depression, and long-term depression [46].

Noordali *et al.* [47] conducted a systematic review that evaluated the effectiveness of mindfulness-based cognitive therapy (MBCT) in depressed or distressed people with diabetes. They included 11 studies that satisfied the inclusion criteria. Seven studies were RCTs, with the remainder having either an observational or quasi-experimental design. MBCT had mixed effects on physiological outcomes (HbA_{1c} and blood pressure), but appeared to reduce depression, anxiety and distress symptoms across several studies [47].

A systematic review evaluated the cost-effectiveness of treatment of depression [48]. Only four economic evaluations were found but these studies reported that interventions reduced depression and were cost-effective compared with care as usual [48]. These studies were all conducted in the USA and evaluated collaborative care programmes that included psychological therapies. Two studies reported that costs per quality-adjust life year (QALY) gained were US $267–4317; moreover, the other two studies described net savings of $440–612 with the intervention and net gains in depression free days or QALYs [48].

Putting the evidence into practice

There is trial evidence showing that we can effectively treat depression in diabetes. But how can we put the evidence into practice? In a recent review article, Petrak *et al.* [44] recommended a stepped care model, based on the current scientific literature (Fig. 1). In that model [44], assessment of depression severity and persistence of symptoms is a key task that determines the treatment approach. It is also crucial that the treatment response is monitored during all phases of this stepped-care approach, and suicidal ideation is guarded continuously at every step of care.

Step 1: subthreshold depressive symptoms that cause impairment

If suicidal ideation and acute crisis are ruled out, interventions for mild depression could probably be offered within primary care. This could include giving self-help materials or using an app- or web-based intervention that targets depression in people with diabetes. In case of a positive history of severe, recurrent depression, selective serotonin-reuptake inhibitors (SSRIs) or psychotherapy are to be considered. Depressive symptoms should be monitored carefully over 2–4 weeks; if no improvement is noted, treatment as described in step 2 is indicated.

Step 2: moderate depression (or persistent mild depression that does not respond to step 1)

Specific treatment for depression is advised in case of persistent mild or moderate depression. Information should be given about different psychological and pharmacological treatment options that include CBT and SSRIs. For people with recurrent depression, medication combined with psychotherapy is recommended. In case of non-remission observed after 2–4 weeks of treatment, the dose should be increased or the type of drug can be changed.

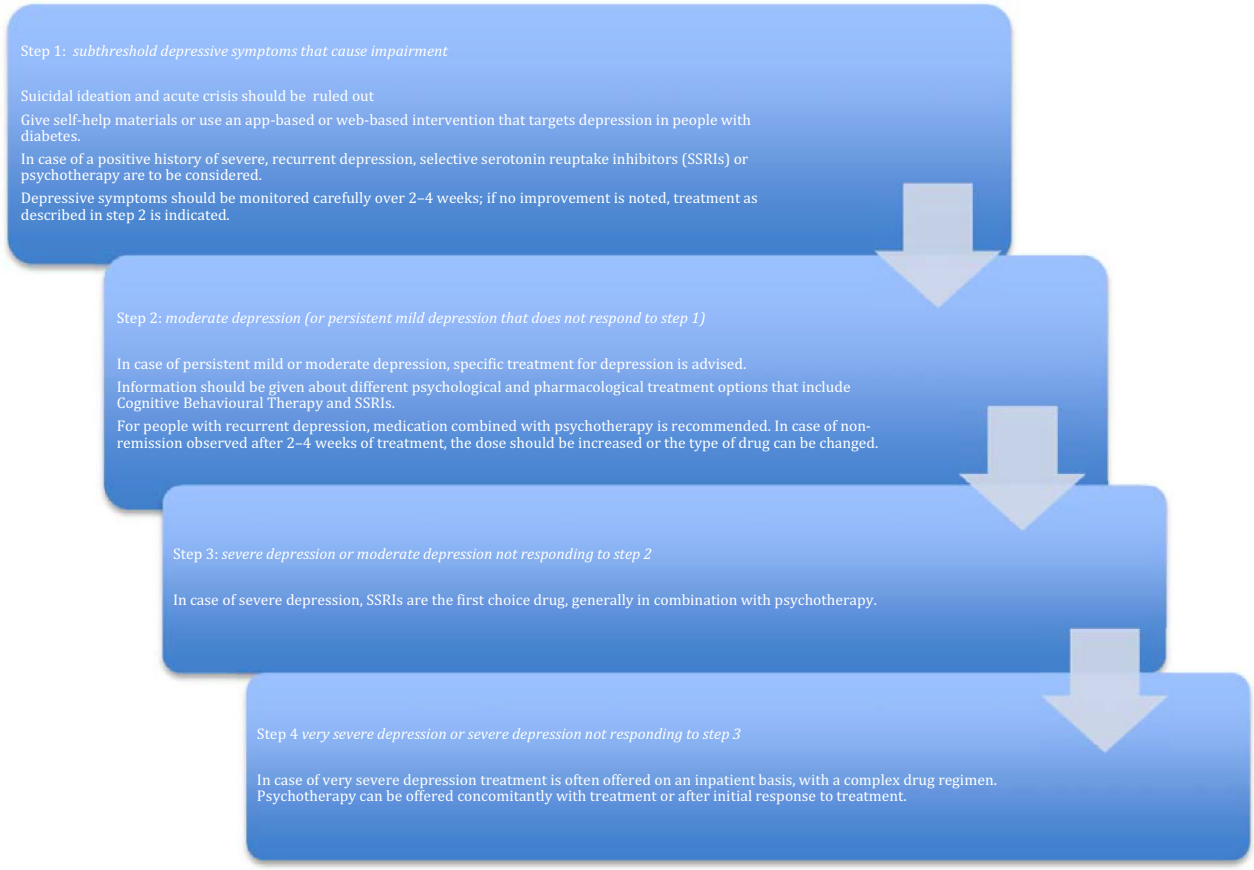

FIGURE 1 Stepped care model for depression in diabetes as described by Petrak *et al*. [44].

Step 3: severe depression or moderate depression not responding to step 2

In case of severe depression, SSRIs are the first choice drug, generally in combination with psychotherapy.

Step 4: very severe depression or severe depression not responding to step 3

In case of very severe depression, treatment is often offered on an inpatient basis, with a complex drug regimen. Psychotherapy can be offered concomitantly with treatment or after initial response to treatment.

When treating comorbid depression in diabetes, it is important to take coexisting diabetes-distress into account. The term diabetes-distress is used to describe a person's emotional responses to the burden of living with a largely self-managed chronic disease and its debilitating complications, and comprises worries about hypoglycaemia, feeling overwhelmed by diabetes, or feelings of guilt or anxiety when one gets off track with diabetes management [49]. For people with diabetes and depression who are also seriously distressed about their diabetes, depression treatment should incorporate these concerns [49]. These individuals should receive an integrated treatment, in which the diabetes professionals (general practitioners, nurse practitioners and endocrinologists) and mental health professionals (psychologists and psychiatrists) closely collaborate in a multidisciplinary context [49].

Despite our increased knowledge on the treatment of depression in diabetes, depression appears to be highly persistent and/or recurrent in type 2 diabetes. This suggests that in people with type 2 diabetes depression remains unnoticed and thus untreated, or that depression is resistant to currently available treatments, or both [25]. Further knowledge on the potentially common ground between the co-existence of depression and diabetes can further improve their clinical management. Psychosocial guidelines have existed for many years in many countries, but are often not applied in clinical practice. Therefore, further work is also needed to support successful implementation of routine assessments in clinical practice of psychological problems including depression, with subsequent treatment if needed.

Future research

Meta-analyses have concluded that depression is linked to an increased risk of developing type 2 diabetes. However, a narrative review of longitudinal studies suggested that not only depression, but also other psychological problems such as general emotional stress, sleeping problems, anger and

hostility are associated with an increased risk of developing type 2 diabetes [50]. For several other psychological factors, such as childhood neglect or other adverse life events and elevated work stress, findings were conflicting [50]. Using cross-sectional data from surveys of 52 095 community-dwelling adults in 19 countries, De Jonge *et al.* [51] found that 16 DSM-IV disorders were associated with a diagnosis of diabetes in bivariate models, but after comorbidity adjustment only binge eating disorder (OR 2.6; 95% CI 1.7, 4.0), bulimia nervosa (OR 2.1; 95% CI 1.3, 3.4) intermittent explosive disorder (OR 1.6; 95% CI 1.1, 2.1) and depression (OR 1.3; 95% CI 1.1, 1.5) remained [51]. Future longitudinal studies should thus not only study depression as a risk factor of diabetes, but also focus on other psychiatric disorders [52]. Future studies should also focus on the role and treatment of subtypes of depression, such as atypical depression, melancholic depression, anxious depression and the role of co-morbid diabetes-related distress [49], while developing new web- and app-based interventions for depression and diabetes-related distress in people with diabetes [49,53]. It is clear that psychological and pharmacological treatments positively impact depression outcomes in people with diabetes shortly after treatment and there are short-term improvements in glycaemic control in pharmacological trials. However, there is still a lack of long-term follow-up, which limits the evidence on the sustainability of treatment effects [54] and its cost-effectiveness. It still unclear whether intensive treatment of depression in diabetes, and perhaps comorbid diabetes-related distress can improve future health outcomes by reducing the risk of developing microvascular or macrovascular complications.

Conclusion

In the past 25 years, knowledge about the complex associations between depression and diabetes, and how to treat this common and important clinical problem has increased considerably. Although it is clear that depression in individuals with diabetes is associated with less optimal diabetes self-care, higher HbA_{1c}, impaired quality of life, incident micro- and macrovascular complications, and elevated mortality rates, it is unclear whether intensive treatment of depression in diabetes reduces the risk of developing diabetes complications or prolongs life. Future studies should also investigate the biological and behavioural mechanisms that link both conditions and test innovative diabetes-specific e-health interventions for depression in diabetes.

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References

1 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5). Washington, DC: American Psychiatric Association, 2013.
2 Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet* 2007; **370**: 851–858.
3 Willis T. *Pharmaceutice rationalis sive diatriba de medicamentorum operationibus in humano corpore*. Oxford: E Theatro Sheldoniano, 1675.
4 Gavard JA, Lustman PJ, Clouse RE. Prevalence of depression in adults with diabetes. An epidemiological evaluation. *Diabetes Care* 1993; **16**: 1167–1178.
5 Lustman PJ, Griffith LS, Gavard JA, Clouse RE. Depression in adults with diabetes. *Diabetes Care* 1992; **15**: 1631–1639.
6 Jacobson AM. Depression and diabetes. *Diabetes Care* 1993; **16**: 1621–1623.
7 Eaton WW, Armenian H, Gallo J, Pratt L, Ford DE. Depression and risk for onset of type II diabetes. A prospective population-based study. *Diabetes Care* 1996; **19**: 1097–1102.
8 Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia* 2006; **49**: 837–845.
9 Rotella F, Mannucci E. Depression as a risk factor for diabetes: a meta-analysis of longitudinal studies. *J Clin Psychiatry* 2013; **74**: 31–37.
10 Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001; **24**: 1069–1078.
11 Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabet Med* 2006; **23**: 1165–1173.
12 Barnard KD, Skinner TC, Peveler R. The prevalence of co-morbid depression in adults with Type 1 diabetes: systematic literature review. *Diabet Med* 2006; **23**: 445–448.
13 Nouwen A, Nefs G, Caramlau I, Connock M, Winkley K, Lloyd CE *et al.* Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: a systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium. *Diabetes Care* 2011; **34**: 752–762.
14 Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. *J Affect Disord* 2012; **142**(Suppl): S8–S21.
15 Buchberger B, Huppertz H, Krabbe L, Lux B, Mattivi JT, Siafarikas A. Symptoms of depression and anxiety in youth with type 1 diabetes: a systematic review and meta-analysis. *Psychoneuroendocrinology* 2016; **70**: 70–84.
16 Sun JC, Xu M, Lu JL, Bi YF, Mu YM, Zhao JJ *et al.*; Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal (REACTION) Study group. Associations of depression with impaired glucose regulation, newly diagnosed diabetes and previously diagnosed diabetes in Chinese adults. *Diabet Med* 2015; **32**: 935–943.
17 Weikert B, Buttery AK, Heidemann C, Rieckmann N, Paprott R, Maske UE *et al.* Glycaemic status and depressive symptoms among adults in Germany: results from the German Health Interview and

Examination Survey for Adults (DEGS1). *Diabet Med* 2018; **35**: 1552–1561.
18 Li Z, Guo X, Jiang H, Sun G, Sun Y, Abraham MR. Diagnosed but not undiagnosed diabetes is associated with depression in rural areas. *Int J Environ Res Public Health* 2016; **13**. pii: E1136.
19 Meurs M, Roest AM, Wolffenbuttel BH, Stolk RP, de Jonge P, Rosmalen JG. Association of depressive and anxiety disorders with diagnosed versus undiagnosed diabetes: an epidemiological study of 90,686 participants. *Psychosom Med* 2016; **78**: 233–241.
20 Harding KA, Pushpanathan ME, Whitworth SR, Nanthakumar S, Bucks RS, Skinner TC. Depression prevalence in Type 2 diabetes is not related to diabetes–depression symptom overlap but is related to symptom dimensions within patient self-report measures: a meta-analysis. *Diabet Med* 2019; **36**: 1600–1611.
21 Fisher L, Hessler DM, Polonsky WH, Masharani U, Peters AL, Blumer I *et al*. Prevalence of depression in Type 1 diabetes and the problem of over-diagnosis. *Diabet Med* 2016; **33**: 1590–1597.
22 Kampling H, Petrak F, Farin E, Kulzer B, Herpertz S, Mittag O. Trajectories of depression in adults with newly diagnosed type 1 diabetes: results from the German Multicenter Diabetes Cohort Study. *Diabetologia* 2017; **60**: 60–68.
23 Nouwen A, Winkley K, Twisk J, Lloyd CE, Peyrot M, Ismail K *et al*. European Depression in Diabetes (EDID) Research Consortium. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia* 2010; **53**: 2480–2486.
24 Chireh B, Li M, D'Arcy C. Diabetes increases the risk of depression: a systematic review, meta-analysis and estimates of population attributable fractions based on prospective studies. *Prev Med Rep* 2019; **14**: 100822.
25 Nefs G, Pouwer F, Denollet J, Pop V. The course of depressive symptoms in primary care patients with type 2 diabetes: results from the Diabetes, Depression, Type D Personality Zuidoost-Brabant (DiaDDZoB) Study. *Diabetologia* 2012; **55**: 608–616.
26 Schram MT, Baan CA, Pouwer F. Depression and quality of life in patients with diabetes: a systematic review from the European depression in diabetes (EDID) research consortium. *Curr Diabetes Rev* 2009; **5**: 112–119.
27 Nouwen A, Adriaanse MC, van Dam K, Iversen MM, Viechtbauer W, Peyrot M *et al*. European Depression in Diabetes (EDID) Research Consortium. Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. *Diabet Med* 2019; **36**: 1562–1572.
28 Van Dooren FE, Nefs G, Schram MT, Verhey FR, Denollet J, Pouwer F. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PLoS One* 2013; **8**: e57058.
29 Elamoshy R, Bird Y, Thorpe L, Moraros J. Risk of depression and suicidality among diabetic patients: a systematic review and meta-analysis. *J Clin Med* 2018; **7**. pii: E445.
30 Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ *et al*. Depression and diabetes treatment non-adherence: a meta-analysis. *Diabetes Care* 2008; **31**: 2398–2403.
31 Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. *Lancet Diabetes Endocrinol* 2015; **3**: 461–471.
32 Brown SA, García AA, Brown A, Becker BJ, Conn VS, Ramírez G *et al*. Biobehavioral determinants of glycemic control in type 2 diabetes: a systematic review and meta-analysis. *Patient Educ Counsel* 2016; **99**: 1558–1567.
33 Herder C, Hermanns N. Subclinical inflammation and depressive symptoms in patients with type 1 and type 2 diabetes. *Semin Immunopathol* 2019; **41**: 477–489.
34 Van Agtmaal MJM, Houben AJHM, Pouwer F, Stehouwer CDA, Schram MT. Association of microvascular dysfunction with late-life depression: a systematic review and meta-analysis. *JAMA Psychiatry* 2017; **74**: 729–739.
35 Kan C, Pedersen NL, Christensen K, Bornstein SR, Licinio J, MacCabe JH *et al*. Genetic overlap between type 2 diabetes and depression in Swedish and Danish twin registries. *Mol Psychiatry* 2016; **21**: 903–909.
36 Haljas K, Amare AT, Alizadeh BZ, Hsu YH, Mosley T, Newman A *et al*. Bivariate genome-wide association study of depressive symptoms with type 2 diabetes and quantitative glycemic traits. *Psychosom Med* 2018; **80**: 242–251.
37 Clarke TK, Obsteter J, Hall LS, Hayward C, Thomson PA, Smith BH *et al*. Investigating shared aetiology between type 2 diabetes and major depressive disorder in a population based cohort. *Am J Med Genet B Neuropsychiatr Genet* 2017; **174**: 227–234.
38 Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry* 2013; **18**: 963–974.
39 Hoogendoorn CJ, Roy JF, Gonzalez JS. Shared dysregulation of homeostatic brain–body pathways in depression and type 2 diabetes. *Curr Diab Rep* 2017; **17**: 90.
40 Barnard K, Peveler RC, Holt RI. Antidepressant medication as a risk factor for type 2 diabetes and impaired glucose regulation: systematic review. *Diabetes Care* 2013; **36**: 3337–3345.
41 Pan A, Sun Q, Okereke OI, Rexrode KM, Rubin RR, Lucas M *et al*. Use of antidepressant medication and risk of type 2 diabetes: results from three cohorts of US adults. *Diabetologia* 2012; **55**: 63–72.
42 Kivimäki M, Batty GD, Jokela M, Ebmeier KP, Vahtera J, Virtanen M *et al*. Antidepressant medication use and risk of hyperglycemia and diabetes mellitus: a noncausal association? *Biol Psychiatry* 2011; **70**: 978–984.
43 de Joode JW, van Dijk SEM, Walburg FS, Bosmans JE, van Marwijk HWJ, de Boer MR *et al*. Diagnostic accuracy of depression questionnaires in adult patients with diabetes: a systematic review and meta-analysis. *PLoS One* 2019; **14**: e0218512.
44 Petrak F, Baumeister H, Skinner TC, Brown A, Holt RIG. Depression and diabetes: treatment and health-care delivery. *Lancet Diabetes Endocrinol* 2015; **3**: 472–485.
45 Van der Feltz-Cornelis CM, Nuyen J, Stoop C, Chan J, Jacobson AM, Katon W *et al*. Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis. *Gen Hosp Psychiatry* 2010; **32**: 380–395.
46 Uchendu C, Blake H. Effectiveness of cognitive–behavioural therapy on glycaemic control and psychological outcomes in adults with diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Diabet Med* 2017; **34**: 328–339.
47 Noordali F, Cumming J, Thompson JL. Effectiveness of Mindfulness-based interventions on physiological and psychological complications in adults with diabetes: a systematic review. *J Health Psychol* 2017; **22**: 965–983.
48 Jeeva F, Dickens C, Coventry P, Bundy C, Davies L. Is treatment of depression cost-effective in people with diabetes? A systematic review of the economic evidence. *Int J Technol Assess Health Care* 2013; **29**: 384–391.
49 Snoek FJ, Bremmer MA, Hermanns N. Constructs of depression and distress in diabetes: time for an appraisal. *Lancet Diabetes Endocrinol* 2015; **3**: 450–460.
50 Pouwer F, Kupper N, Adriaanse MC. Does emotional stress cause type 2 diabetes mellitus? A review from the European Depression in Diabetes (EDID) Research Consortium. *Discov Med* 2010; **9**: 112–118.
51 De Jonge P, Alonso J, Stein DJ, Kiejna A, Aguilar-Gaxiola S, Viana MC *et al*. Associations between DSM-IV mental disorders and

diabetes mellitus: a role for impulse control disorders and depression. *Diabetologia* 2014; **57**: 699–709.
52 Lindekilde N, Nefs G, Henriksen JE, Lasgaard M, Schram M, Rubin K *et al*. Psychiatric disorders as risk factors for the development of type 2 diabetes mellitus: an umbrella review protocol. *BMJ Open* 2019; **9**: e024981.
53 Van Bastelaar KM, Pouwer F, Cuijpers P, Riper H, Snoek FJ. Web-based depression treatment for type 1 and type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care* 2011; **34**: 320–325.
54 Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus: an abridged Cochrane review. *Diabet Med* 2014; **31**: 773–786.